Marta Pascual´s Project

The role of septohippocampal connection and GABAergic interneurons in Alzheimer's disease.

Alzheimer's disease (AD) causes synaptic loss, alterations in the balance of neuronal activity and cognitive deficits. Recently, we have shown a clear diminution of septal GABAergic synaptic contacts on GABAergic hippocampal neurons in AD, associated with a significant alteration of hippocampal oscillatory rhythms.

The septohippocampal (SH) connection consists of two major components: the cholinergic and the GABAergic. Both contact segregated and specifically to their target cells in the hippocampus. GABAergic SH connection controls the synchronous activity of the hippocampus, including theta rhythms, responsible for processing visuospatial memory, disrupted in AD. Following our most recent data (Rubio et al., 2012, Soler et al., submitted) that showed alterations of GABAergic SH connection both in response to the accumulation of amyloid-β (Aβ) (J20 mice) and also in the presence of hyperphosphorylated forms of Tau (P-tau) (VLW mice), we are interested in analysing histologically and functionally whether Aβ and P-Tau act synergistically using a transgenic mice model which exhibit the accumulation of both compounds (J20-VLW mice).

It has been suggested that a dysfunction of hippocampal interneurons could be the responsible for abnormalities in the oscillatory rhythms, excitability as well as cognitive deficits associated with AD. Our current hypothesis is that an optogenetic or a pharmacological intervention able to restore the interneuronal activity in animal models of AD, could regulate inhibitory synaptic activity in the hippocampus, which in turn could restore synchronous hippocampal activity, and therefore produce cognitive improvement.

Our main objectives are:

1) To analyse the synergic effect of Aβ and P-Tau in AD development.
2) To characterize the function of hippocampal interneurons in AD.
3) To use optogenetics to analyse the impact of stimulation/inhibition of GABAergic SH neurons in the hippocampal physiology, and its use as a therapeutic strategy for AD.

To perform these projects, we use multidisciplinary approaches that includes:
histology, tracing methods, optogenetics, electron microscopy, organotypic cultures, electrophysiological techniques, and cognitive tests.

Personal:

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Selected publications:

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Soriano E, Pascual M, Gruart A, Delgado-García JM. **The GABAergic septohippocampal pathway is directly involved in internal processes related to operant reward learning.** Cereb Cortex. 2014 Aug;24(8):2093-107.

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